REMARKS

Claims 1-3 and 5-23 were pending in this application. Applicants have canceled claims 1-12, 15 and 18 without prejudice and amended claims 13, 16-17 and 21-23 to more clearly point out certain embodiments of the present invention. Applicants fully reserve the right to prosecute the canceled subject matter in one or more related applications. Upon entry of the present amendments, claims 13-14, 16-17 and 19-23 will be pending in the present application.

Specifically, claim 13 has been amended to include the recitation of canceled claims 15 and 18. Support for amended claim 13 can be found in the patent application publication at, *inter alia*, paragraphs [0008]-[0010], [0015]-[0016], [0024], [0065], [0143]-[0144] and [0151]; Fig. 1, Fig. 2, and Fig. 7; Examples 1-9; and claims 1, 3, 7 and 11 as originally filed. Claims 16-17 and 21-22 have been amended to correct certain editorial errors. The dependency of claim 23 has been amended. No new matter has been added.

I. THE PRESENT INVENTION

The presently claimed invention, as recited in amended independent claim 13, relates to a method of screening to identify a gene, whose function was unknown previously, as a target for drug development by using a combination of high-density oligonucleotide array and *in situ* hybridization to identify those mRNAs and/or expression sequence tags ("ESTs") whose expression level and localization have both changed in response to an event. In said method, first, a high-density oligonucleotide array is used to examine the expression level of mRNAs and/or ESTs before and after an event and a scatter diagram is made to show the changes in expression levels (step (a)). Second, one or more mRNAs and/or ESTs whose expression level has changed in response to the event are identified based on the results in the scatter diagram and from databases searches (step (b)). Third, a probe that will specifically hybridize with the identified mRNA and/or EST whose expression level has changed in response to the event is designed (step (c)). Fourth, the probe is used to perform an *in situ* hybridization of at least two types of different tissues or cells of an organism before and after the event (step (d)). Fifth, the localization of the mRNA and/or EST in the tissues or cells is examined before and after the event (step (e)). Sixth, those mRNAs and/or ESTs whose localization has changed in response to the event are identified (step (f)). Finally, those mRNAs and/or ESTs whose expression level and localization have both changed in response to the event are identified as targets for drug development (step (g)). The present invention provides a novel, efficient and systemic method for screening and identifying genes with

previously unknown functions that are useful for drug development.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

The Office Action states that the rejection of claims 1, 2, 11 and 12 under 35 U.S.C. § 102(b) as being anticipated by Toran-Allerand (U.S. Patent No. 5,990,078) is maintained. Applicants submit that claims 1, 2, 11 and 12 have been canceled and, therefore, the rejection is rendered moot. The Office Action also states that claims 6-8, 13-14, 17-19, 21 and 22 are rejected under 35 U.S.C. § 102(b) as being anticipated by Toran-Allerand. Applicants submit that claims 6-8 and 18 have also been canceled and, therefore, the rejection is rendered moot with respect to claims 6-8 and 18.

While Applicants do not agree and in no way acquiesce with the rejection of the remaining claims and solely to expedite prosecution, Applicants have amended claim 13 to more clearly describe certain embodiments of the present invention. In particular, Applicants have amended claim 13 to include the recitation of previously pending claim 15, which was not rejected as being anticipated by Toran-Allerand. For the following reasons, Applicants submit that claims 13-14, 17, 19 and 21-22 are novel and nonobvious over Toran-Allerand.

Toran-Allerand describes a method of increasing the level of estrogen receptors in a neural tissue sample from a subject by contacting the sample with estrogen and a neurotrophin, so as to thereby increase the level of estrogen receptors in the sample (col. 5, lines 37-44). The sequence and function of estrogen receptor mRNA were well known (col. 1, lines 24-33); it was also known in the art that estrogen receptor mRNA was present in adult dorsal root ganglion (DRG) neurons *in vivo* (col. 2, lines 26-30).

"A claim is anticipated only if *each and every* element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2USPQ2d 1051, 1053 (Fed. Cir. 1987) (emphasis added).

Toran-Allerand does not describe the use of high-density oligonucleotide array as recited in step (a) of amended claim 13 to show changes in expression levels of the mRNAs and EST before and after the event. Toran-Allerand never mentions the use of a DNA chip or DNA microarray, such as a high-density oligonucleotide array, to study the expression of genes, much less teach or suggest the use of a scatter diagram to analyze the probing of the array (also recited in step (a) of amended claim 13). Moreover, Toran-Allerand does not describe the combined use of high-density oligonucleotide array with *in situ* hybridization.

At most, Toran-Allerand describes the use of *in situ* hybridization to examine expression level of estrogen receptor mRNA and the estrogen binding in PC12 cells (col. 13, lines 27-30). In contrast, the present invention examines expression levels of genes using a high-density oligonucleotide array while using *in situ* hybridization to examine the localization of genes.

The Office Action states that the function of the estrogen receptor mRNA and neurotrophin receptor in reciprocal regulation in response to an event is unknown and is the target of investigation by Toran-Allerand (page 5, lines 8-11). Nevertheless, Toran-Allerand does not describe screening and identifying genes *per se*. Rather, Toran-Allerand specifically studies the expression of estrogen receptor mRNA and neurotrophin receptor mRNA in the nerve cell PC12. In contrast, the claimed method relates to the screening and identification of genes with unknown function, not the further characterization of genes with already known functions.

Because Toran-Allerand fails to teach or suggest each and every element of amended claim 13, Applicants submit that the presently claimed invention comprises key features that are not anticipated by the disclosure of Toran-Allerand. All claims that depend from claim 13 also recite the limitations of canceled claim 15, which recite features that Toran-Allerand failed to teach or suggest. As such, the present invention is novel and nonobvious over Toran-Allerand and the rejection based on this reference cannot stand.

In view of the foregoing, Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 102(b) be withdrawn.

II. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 102(e) SHOULD BE WITHDRAWN

1. The Invention is Novel and Nonobvious Over Joly et al.

The Office Action states that the rejection of claims 1 and 3 under 35 U.S.C. § 102(e) as being anticipated by Joly et al. (U.S. Patent No. 6,342,495) are maintained. Applicants submit that claims 1 and 3 have been canceled and, therefore, the rejection is rendered moot. The Office Action also states that claims 5 and 7-10 are rejected under 35 U.S.C. § 102(e) as being anticipated by Joly et al. Applicants submit that claims 5 and 7-10 have also been canceled and, therefore, the rejection is rendered moot. Applicants respectfully request that the rejection be withdrawn.

2. **The Invention is Novel and Nonobvious Over Gonzalez-Zulueta et al.**

The Office Action states that claims 13-16 and 18-23 are rejected under 35 U.S.C. § 102(e) as being anticipated by Gonzalez-Zulueta et al. (U.S. Patent No. 6,670,138). Applicants submit that claims 15 and 18 have been canceled and, therefore, the rejection is rendered moot with respect to claims 15 and 18. For the following reasons, Applicants submit that claims 13-14, 16 and 19-23 are novel and nonobvious over Gonzalez-Zulueta et al.

As a preliminary matter, Applicants submit that Gonzalez-Zulueta et al. does not qualify as prior art against the present invention. This application claims the benefit of priority under 35 U.S.C. § 119(a) to Japanese Patent Application No. 2001-112367, filed April 11, 2001. Gonzalez-Zulueta et al. was published on December 30, 2003 and has a filing date of October 31, 2001, which is after the priority date of the present application. Accordingly, Applicants submit that Gonzalez-Zulueta et al. has been improperly cited as prior art under 35 U.S.C. § 102(e).

Gonzalez-Zulueta et al. describes methods for diagnosing the occurrence of a stroke or assessing a patient's susceptibility to a stroke by detecting in a patient sample an elevated level of UCP-2 expression (col. 2, lines 64-67). Like Toran-Allerand, Gonzalez-Zulueta et al. does not describe the use of high-density oligonucleotide array to make a scatter diagram as recited in step (a) of amended claim 13 to show changes in expression levels of the mRNAs and EST before and after the event. Moreover, Gonzalez-Zulueta et al. does not describe the combined use of high-density oligonucleotide array with *in situ* hybridization to lead drug research and development in a more correct direction and therefore, reduce the time and cost required for drug research and development (see paragraph [0021] of the specification).

While the Office Action states that Gonzalez-Zulueta et al. teaches the method of claim 13, wherein expression of the mRNA is confirmed with a microarray (page 16, lines 18-19). Applicant submits that no evidence has been provided to substantiate that allegation.

Gonzalez-Zulueta et al. identifies the altered expression of the gene by subtractive hybridization and then teaches diagnostic methods for detecting altered UCP-2 expression by a number of techniques, *e.g.*, *in situ* hybridization, Northern blots, nucleic acid probe arrays, etc. (col. 20, lines 43-50; and Example 1). Gonzalez-Zulueta et al. does not teach the use of arrays to screen genes of unknown function. Gonzalez-Zulueta et al. also does not contemplate the use of a combination of techniques to screen for new drug target candidates. At most, Gonzalez-Zulueta et al. mentions nucleic acid probe arrays in a generic fashion for use in the diagnostic methods based upon the already identified target, UCP-2 (col. 20, line

28 to col. 21, line 30). There is no teaching in Gonzalez-Zulueta et al. to specifically use a high-density oligonucleotide array such as GENECHIP™, much less combining the use of a high-density oligonucleotide array with *in situ* hybridization to examine both the expression level and localization of genes.

Furthermore, Applicants submit that making a scatter diagram and analyzing the scatter diagram and database searches is a further improvement achieved by the present inventors (see paragraph [0065] of the specification), and these techniques cannot obtain from the GENECHIP™ technique alone that was generically mentioned in Gonzalez-Zulueta et al.

As such, the present invention is novel and nonobvious over Gonzalez-Zulueta et al. and the rejection based on this reference cannot stand and must be withdrawn.

Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 102(e) be withdrawn.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112 SHOULD BE WITHDRAWN

The Office Action states that claims 1-3, 5-12 and 15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants submit that claims 1-3, 5-12 and 15 have been canceled and, therefore, the rejection is rendered moot and should be withdrawn.

The Office Action states that the phrase "used for screening of a gene encoding a substance effective as a drug" in previously pending claim 8 is confusing because it is unclear how one is to establish whether a gene encodes a substance effective as a drug when the function of the gene is unknown. The test of definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Orthokinetic Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1 USPQ2d 1081 (C.A.F.C. 1986); see also MPEP § 2106 (V)(A)(2). Applicants submit that one skilled in the art, when reading the claim in light of the specification, would understand that a substance encoded by a gene may be shown to possess certain pharmacological properties, thus making it potentially useful as a drug. In particular, the specification provides a number of non-limiting examples in which a gene screened by the presently claimed method may encode a substance useful as a drug (see, *e.g.*, paragraph [0024], especially on page 2, right column, lines 12-19). As such, Applicants submit that claim 19, which recites the phrase, is neither confusing nor indefinite.

CONCLUSION

In light of the submissions herewith, the above remarks and amendments, it is submitted that all outstanding rejections have been overcome. Attorneys for Applicants respectfully submit that the claims fully meet all statutory requirements for patentability. Withdrawal of the rejections and allowance of claims 13-14, 16-17 and 19-23 are respectfully requested. Should the Examiner not agree with Applicants' position, then a telephonic interview is respectfully requested to discuss any remaining issues and expedite the eventual allowance of the application.

Respectfully submitted,

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(Reg. No.)

Margaret B. Brivanlou
JONES DAY
222 East 41st Street
New York, New York 10017-6702
(212) 326-3939